

IN THE CLAIMS:

Claim 1 (currently amended) A pharmaceutical composition for the treatment of a disease involving active angiogenesis which comprises (a) a tubulin binding agent in an amount sufficient to cause damage to neovaasculature, together with (b) an inhibitor of the formation of nitric oxide in a mammalian system and (c) a pharmaceutically acceptable excipient.

Claim 2 (currently amended) A pharmaceutical composition for the damage of the formation of new vasculature by angiogenesis comprising a combination of (a) a tubulin binding agent in an amount sufficient to cause damage to neovasculature, (b) an inhibitor of nitric oxide synthase in an amount sufficient to augment the effect of the tubulin binding agent and (c) a pharmaceutically acceptable excipient.

Claim 3 (cancelled)

Claim 4 (previously presented) A composition according to claim 2 wherein the inhibitor of nitric oxide synthase is selected from a derivative of arginine, ornithine, lysine, citrulline, S-alkylthioureas and aminoguanidine.

Claim 5 (original) A composition according to claim 4 wherein the nitric oxide synthase inhibitor is an N<sup>G</sup>-substituted L-arginine selected from N<sup>G</sup>-nitro-L-arginine and alkyl esters thereof, N<sup>G</sup>-methyl-L-arginine and N<sup>G</sup>-amino-L-arginine.

Claim 6 (original) A composition according to claim 4 wherein the derivative of

ornithine is L-N6-(1-iminoethyl)-ornithine.

Claim 7 (original) A composition according to claim 4 wherein the derivative of lysine is L-N6-(1-iminoethyl)-lysine.

Claim 8 (previously presented) A composition according to claim 4 wherein the derivative of citrulline is selected from L-thiocitrulline, L-homothiocitrulline or an S-alkylthiocitrulline.

Claim 9 (cancelled)

Claim 10 (previously presented) A composition according to claim 1 wherein the composition is in the form of a kit, one part of the kit containing the tubulin binding agent and the second part of the kit the inhibitor of the formation of nitric oxide.

Claims 11 and 12 (cancelled)

Claim 13 (currently amended) A method of treatment for a mammal having a disease involving active angiogenesis with the formation of new vasculature in the mammal, said method comprising administration to the mammal of a tubulin binding agent and an inhibitor of formation of nitric oxide, the tubulin binding agent being administered to the mammal in an amount effective to cause damage to the new vasculature. the inhibitor of formation of nitric oxide being administered to the mammal in an amount sufficient to augment the effect of the tubulin binding agent.

Claim 14 (previously presented) A method according to claim 13 wherein the tubulin binding agent and inhibitor of the formation of nitric oxide are administered substantially simultaneously but separately to the mammal under treatment.

Claims 15 to 20 (cancelled)

Claim 21 (previously presented) A composition according to claim 4 wherein the derivative of citrulline is S-methyl-L-thiocitrulline.

Claims 22 and 23 (canceled)

Claim 24 (previously presented) A composition according to claim 1 or claim 2 wherein the tubulin binding agent is selected from N-acetylcolchinol and its prodrugs.

Claim 25 (previously presented) A composition according to claim 1 or claim 2 wherein the tubulin binding agent is N-acetylcolchinol-O-phosphate.

Claim 26 (previously presented) A composition according to claim 1 or claim 2 wherein the tubulin binding agent is selected from combretastatin A4 and its prodrugs.

Claim 27 (previously presented) A composition according to claim 1 or claim 2 wherein the tubulin binding agent is selected from combretastatin A4 phosphate.

Claim 28 (previously presented) A composition according to claim 1 or claim 2 wherein

the tubulin binding agent is selected from (Z)-2 methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenylamine and its prodrugs.

Claim 29 (previously presented) A composition according to claim 2 wherein the inhibitor of nitric oxide synthase is an aminopyridin .

Claim 30 (previously presented) A composition according to claim 2 wherein the inhibitor of nitric oxide synthase is 2-amino-4-methylpyridine.

Claim 31 (previously presented) A composition according to claim 2 wherein the tubulin binding agent is selected from N-acetylcolchicol and its prodrugs, or combretastatin A4 and its prodrugs and wherein the inhibitor of nitric oxide synthase is selected from N<sup>G</sup>-nitro -L-arginine or an alkyl ester thereof, N<sup>G</sup>-methyl-L-arginine, N<sup>G</sup>-amino-L-arginine, L-N6-(1-iminoethyl)ornithine, L-N6-(1-iminoethyl)-lysine, L-thiocitrulline, L-homothiocitrulline, S-alkylthiocitrulline and 2- amino-4-methylpyridine.

Claim 32 (previously presented) A composition according to claim 2 wherein the tubulin binding agent is selected from N-acetylcolchicol and its prodrugs, or combretastatin A4 and its prodrugs, and wherein the inhibitor of nitric oxide synthase is selected from N<sup>G</sup>-nitro-L-arginine or an alkyl ester thereof and 2-amino-4-methylpyridine.

Claim 33 (currently amended) A method of treatment for a mammal having a cancer involving a solid tumor said method comprising ad administration of a tubulin binding agent and an inhibitor of the formation of nitric oxide in an amount sufficient to augment

the effect of the tubulin binding agent.

Claim 34 (previously presented) A method according to claim 33 wherein the tubulin binding agent and the inhibitor of the formation of nitric oxide are administered substantially simultaneously but separately to the mammal under treatment.

Claim 35 (previously presented) A method according to claim 13 or claim 33 wherein the inhibitor of the formation of nitric oxide is an inhibitor of nitric oxide synthase.

Claim 36 (previously presented) A method according to claim 35 wherein the inhibitor of nitric oxide synthase is selected from a derivative of arginine, ornithine, lysine, citrulline, S-alkylthioureas and aminoguanidine.

Claim 37 (currently amended) A method according to claim 35 wherein the inhibitor of nitric oxide synthase is an N<sup>G</sup>-substituted L-arginine selected from N<sup>G</sup>-nitro-L-arginine and alkyl esters thereof, ~~N<sup>G</sup>- and N<sup>G</sup>-ino-L-arginine~~ N<sup>G</sup>-methyl-L-arginine and N<sup>G</sup>-amino-L-arginine.

Claim 38 (currently amended) A method according to claim ~~37~~ 36 wherein the derivative of ornithine is L-N6-(1-iminoethyl)-ornithine.

Claim 39 (currently amended) A method according to claim ~~37~~ 36 wherein the derivative of lysine is L-N6-(1-iminoethyl)-lysine.

Claim 40 (currently amended) A method according to claim ~~37~~ 36 wherein the derivative of citrulline is selected from L-thiocitrulline, L-homothiocitrulline or an S-alkylthiocitrulline.

Claim 41 (previously presented) A method according to claim 35 wherein the inhibitor of nitric oxide synthase is an aminopyridine.

Claim 42 (previously presented) A method according to claim 35 wherein the inhibitor of nitric oxide synthase is 2-amino-4-methylpyridine.

Claim 43 (previously presented) A method according to claim 13 or claim 33 wherein the tubulin binding agent is selected from N-acetylcolchicinol and its prodrugs.

Claim 44 (previously presented) A method according to claim 13 or claim 33 wherein the tubulin binding agent is N-acetylcolchicinol-O-phosphate.

Claim 45 (previously presented) A method according to claim 13 or claim 33 wherein the tubulin binding agent is selected from combretastin A4 and its prodrugs.

Claim 46 (previously presented) A method according to claim 13 or claim 33 wherein the tubulin binding agent is selected from combretastin A4 phosphate.

Claim 47 (previously presented) A method according to claim 13 or claim 33 wherein the tubulin binding agent is selected from (Z)-2-methoxy-5-[2-(3, 4, 5-

trimethoxyphenyl)vinyl]phenylamine and its prodrugs.

Claim 48 (currently amended) A method according to claim 35 wherein the tubulin binding agent is selected from N-acetylcolchicol and its prodrugs, or combretastatin A4 and its prodrugs and wherein the inhibitor of nitric oxide synthase is selected ~~from~~ from  $\text{N}^{\text{G}}$ -nitro-L-arginine or an alkyl ester thereof,  $\text{N}^{\text{G}}$ -methyl-L-arginine,  $\text{N}^{\text{G}}$ -amino-L-arginine, L-N6-(1-iminoethyl)-ornithine, LN6-(1-iminoethyl)-lysine, L-ihiocitrulline, L-homothiocitrulline, S-alkylthiocitrulline and 2-amino-4-methylpyridine.

Claim 49 (previously presented) A method according to claim 35 wherein the tubulin binding agent is selected from N-acetylcolchicol and is prodrugs, or combretastatin A4 and its prodrugs, and wherein the inhibitor of nitric oxide synthase is selected from  $\text{N}^{\text{G}}$ -nitro-L-arginine or an alkyl ester thereof and 2-amino-4-methylpyridine.

Claim 50 (new). The pharmaceutical composition according to claim 1, wherein the composition consists essentially of the tubulin binding agent, the nitric oxide inhibitor and the pharmaceutically acceptable excipient.